

BIOMEDICAL IMPLICATIONS OF OXYGEN RADICALS

OXYGEN RADICALS IN THE PATHOGENESIS OF EDEMA

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Edema in the lung and other tissues can be induced by agents generating oxygen radicals. Exposure of cultured endothelial cells to xanthine oxidase or t-butylhydroperoxide causes reversible retraction, which in vivo could allow exudation of plasma. The role in this process of oxygen-radical-mediated activation of guanylate cyclase and cyclic AMP phosphodiesterase will be discussed.

Oxy-Radical Production and Cardiotoxicity of Anthracyclines Catalyzed
By Mitochondrial NADH Dehydrogenase

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The anthracyclines adriamycin and daunorubicin are effective chemotherapeutic (anti-cancer) agents whose use is limited by damage to normal cells: Particularly cardiotoxicity. Our results demonstrate that cardiac mitochondrial NADH dehydrogenase mediates a one-electron reduction of adriamycin and daunorubicin to reactive free radicals. The subsequent dismutation of these anthracycline radicals initiates an oxy-radical cascade which, ultimately, results in cellular damage. A new anthracycline derivative, 5-iminodaunorubicin, was found to be essentially unreactive towards NADH dehydrogenase (causing little or no drug, or oxygen radical production), yet demonstrates anti-tumor activity *in vitro*. Thus, 5-iminodaunorubicin may prove to be an effective anti-cancer agent, devoid of cardiotoxic side effects.

LYTIC EFFECTS OF O_2 RADICALS ON RESEALED RBC GHOSTS. A. W. Girotti and J.P. Thomas Department of Biochemistry, The Medical College of Wisconsin, Milwaukee, WI 53226

Resealed erythrocyte (RBC) ghosts containing Na^+ and glucose-6-P (G6P) as markers lyse when exposed to the xanthine/xanthine oxidase/iron system. In the absence of EDTA, marker release accelerates after a lag, Na^+ preceding G6P. Efflux and accompanying thiobarbituric acid-detectable lipid peroxidation (LP) can be totally inhibited by superoxide dismutase (SOD) or catalase (CAT). In the presence of EDTA (2-fold over iron) LP and G6P efflux are reduced to background levels while Na^+ efflux is first order and ~ 3 -fold over background. The latter effect is totally inhibited by CAT, but minimally by SOD. These results suggest that different membrane targets responsible for Na^+ and G6P release have been resolved.